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hormone resistance is found in the case of Laron dwarfism, where growth hormone levels are elevated while somatomedin concentrations are low.<sup>5</sup> It has been suggested that growth hormone may influence erythropoietin<sup>6</sup>; however, this effect is not a pronounced one, nor is it clinically apparent in children with isolated growth hormone deficiency or Laron dwarfism. Unfortunately, measurements of somatomedin were not done in this study to support this possibility.

The catch-up growth that occurred in our patient was associated with a return to normal levels of measurable growth hormone and the onset of puberty. It is, therefore, difficult to separate these influences on the acceleration of the boy's growth, and it is likely that both were needed.<sup>7</sup> The possibility that release of gonadotropin occurred as the result of the brain operation, thereby stimulating puberty is also a consideration. Other authors<sup>8</sup> have reported pituitary insufficiency following radiation therapy to the brain that excludes the pituitary gland.

The accelerated growth seen in patients after removal of lymphoid hamartomas favors a systemic influence. However, no hormonal measurements are available in these studies. Because of the clinical similarity in our patient's course following the operation, a similar mechanism is favored.

### Summary

A brain tumor developed in a 15½-year-old boy with associated arrest of growth (despite the presence of growth hormone) and of sexual maturation, refractory hypochromic anemia and hyperglobulinemia. A similar clinical triad has been reported with lymphoid hamartomas, although the tumor did not resemble this type of tissue growth. After partial removal of the tumor, catch-up growth and sexual maturation occurred with minimal improvement in the anemia. These observations indicate that certain tumors through associated immunological mechanisms have an etiologic role in this clinical pattern.

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## Furosemide and Ethacrynic Acid in Acute Tubular Necrosis

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OLIGURIC ACUTE RENAL FAILURE (ARF) is a syndrome characterized by a rapid decrease in renal function with progressive azotemia and oliguria (urine output of 50 to 400 ml per 24 hours).<sup>1</sup> Major causes of this syndrome are prerenal azotemia (such as volume depletion), postrenal obstruction (such as prostatic hypertrophy), renovascular disease (such as renal artery emboli) and parenchymal renal disease (such as glomerulitis or acute tubular necrosis).<sup>1,2</sup> By far the most common cause of ARF is acute tubular necrosis (ATN), which represents about 75 percent of all cases.<sup>1</sup>

Mannitol has been recommended for both diagnosing and treating ARF, although considerably more is known about the use of the loop diuretics furosemide and ethacrynic acid in this syndrome. It has been proposed that a successful diuresis in response to large intravenous boluses of these latter drugs helps differentiate prerenal azotemia from ATN.<sup>3</sup> Others have suggested that furosemide and ethacrynic acid are effective in

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## ABBREVIATIONS USED IN TEXT

ARF=acute renal failure  
 ATN=acute tubular necrosis  
 GFR=glomerular filtration rate

the treatment of acute tubular necrosis.<sup>4-17</sup> However, serious adverse effects, including permanent deafness, have been attributed to both agents.<sup>18-31</sup> Until now, a thorough discussion of the risks and benefits of using the loop diuretics in the treatment of ATN has not been attempted.

Over the past two years, the Division of Clinical Pharmacology has evaluated two patients with almost identical histories, one of whom is presented below. Both patients became deaf suddenly during diuretic treatment of ATN. Such cases focus physicians' attention on an important question: Do the potential risks of these drugs outweigh their potential benefits in patients with ATN? After examining existing evidence, one can formulate tentative conclusions guiding therapy for similar patients.

### Report of a Case

Septic shock developed five days after an uncomplicated cesarean section in a 25-year-old woman. The 60-kg (132-pound) woman previously had been well. Therapy was begun with clindamycin (300 mg given intravenously every 6 hours) and gentamicin (60 mg given intravenously every 12 hours). Despite administration of fluids intravenously, which restored pulmonary capillary wedge pressure to normal, oliguria developed over the next 12 hours. Administration of gentamicin was discontinued after the second dose; dopamine was given without benefit. Acute tubular necrosis was diagnosed by the medical history, analysis of the urine (many darkly pigmented granular casts) and a renal failure index greater than 5. Two rapid intravenous pushes of furosemide, 120 mg followed by 360 mg several hours later, were given in an unsuccessful attempt to increase urine output. Finally, 150 mg of ethacrynic acid was administered in an intravenous push. Minutes later the patient noted the sudden onset of bilateral deafness, and could hear only shouted commands. There were no vestibular symptoms or signs. Over the next few days, her condition stabilized; sepsis (*Staphylococcus epidermidis* was cultured from blood) responded to oxacillin, and her azotemia resolved com-

pletely. She was discharged home with permanent bilateral sensorineural deafness documented by audiometry.

### Cause of Deafness

The sudden onset of deafness in this case strongly suggests that it was induced by one or more of the three potentially ototoxic medications that the patient received. The first was gentamicin, given in two intravenous doses of 60 mg, each representing 1 mg per kg of body weight. Gentamicin ototoxicity has been well described, occurring in about 2 percent of treatment courses.<sup>32</sup> Vestibular toxicity is more common; however, hearing problems also occur, usually as a gradual hearing loss involving high-range frequencies. Because of the sudden development of deafness, including speech frequency, more than 12 hours after a very modest dose of gentamicin, it is unlikely that this drug is primarily responsible for this defect.

The patient then received furosemide, in two large, rapid intravenous pushes. Furosemide-induced deafness is an uncommon adverse effect, which has been noted in large drug surveillance studies, occurring in less than 0.2 percent of patients receiving "usual" doses (less than 80 mg) for congestive heart failure or edema.<sup>33-35</sup> However, there are now at least eight reported cases of temporary losses of hearing<sup>18,29-31</sup> and six of permanent deafness,<sup>21,27</sup> probably caused by furosemide. Deafness induced by this drug usually occurs suddenly, minutes after a rapid intravenous bolus of more than 100 mg, although doses as low as 60 mg have caused transient deafness.

In every case reported, there was some degree of underlying renal failure, usually ARF. However, intravenously given doses greater than 100 mg are rarely administered for conditions other than acute renal failure. Hearing losses were characterized by increased pure-tone sensorineural hearing thresholds, maximal in the middle range of frequencies.<sup>27,36</sup> The mechanism of furosemide-induced deafness is unknown. Although the half-life of furosemide is increased in patients with renal failure,<sup>37</sup> this would not explain the rapid onset of ototoxicity.

It appears that loss of hearing is related to the rate of administration of furosemide. In a study of 16 uremic patients, Wigand showed that infusion of 1,000 mg of furosemide at 25 mg per minute produced acute reversible hearing loss (documented with both pure-tone and speech

audiograms) in half the subjects, maximal in the middle range of frequencies.<sup>36</sup> A second study with azotemic patients showed that furosemide administered at 25 mg per minute produced "noticeable hearing loss" in 60 percent of the subjects, while infusion at 15 mg per minute produced only "minor hearing losses which the subjects were not aware of."<sup>38</sup>

The third potentially ototoxic drug that the patient received was ethacrynic acid, given just minutes before she suddenly became deaf. Since the first report of ethacrynic acid-induced deafness in 1965,<sup>22</sup> there have been at least 15 reported cases of transient deafness and 11 cases of permanent deafness.<sup>18-20,23-26,28</sup> Administration of ethacrynic acid in "usual" doses (less than 100 mg) to patients in hospital with heart failure or edema resulted in deafness in less than 0.7 percent of treatment courses.<sup>39</sup> Deafness induced by ethacrynic acid usually develops within 15 minutes of a rapid intravenous injection, and has been observed following doses as small as 50 mg.

The mechanism of ethacrynic acid-induced deafness is unclear. Bilateral loss of outer hair cells was noted in one patient at autopsy.<sup>40</sup> A recent study showed that ethacrynic acid caused a large and rapid change in endolymph electrolyte concentrations in dogs.<sup>41</sup> In only ten minutes, ethacrynic acid caused the potassium concentration to decrease from 145 to 21 mEq per liter, while the sodium concentration rose from 5.9 to 143 mEq per liter. The fact that this shift was rapid, large and persistent, and did not occur in the perilymph, suggests that this might be the mechanism for ethacrynic acid-induced deafness.

In summary, this patient's sudden deafness seems to have been caused by a rapid injection of 150 mg of ethacrynic acid. Whether the previous doses of furosemide or gentamicin produced additive or synergistic ototoxicity, an occurrence implied by some authors but never proved, remains an open question.

Other than deafness, the risks of these two diuretics are not great. The most common problems—fluid and electrolyte abnormalities—are seen in 5 percent to 25 percent of patients in hospital who receive conventional doses of the drugs.<sup>33-35,38,42</sup> These adverse effects are reversible, and probably occur less often in oliguric patients who are closely monitored. Other side effects such as nausea, vomiting and epigastric pain occur in less than 10 percent of patients, and are usually transient.<sup>29,33-35,38</sup> Rashes, agranulocytosis

and necrotizing pancreatitis have been reported, but seem to occur only rarely.<sup>43,44</sup>

### Use of Loop Diuretics

Loop diuretics might benefit a patient with acute tubular necrosis in several ways.<sup>1,45,46</sup> First, by decreasing the reabsorption of filtrate in the tubules and increasing intratubular pressure, they might minimize the obstruction of tubules by cell debris and precipitated pigment or proteins. Second, their direct vasodilator effect might reverse the arteriolar vasoconstriction and decreased renal blood flow seen in the early stages of ATN. It is unknown whether tubular leakage of filtrate or decreased glomerular permeability, also found in ATN, are modified by these agents.

Third, it is difficult to ascribe a cause-and-effect relationship between the administration of a diuretic and subsequent diuresis. Muth<sup>47</sup> described almost identical clinical courses in two patients with ATN. In both patients a sudden brisk, sustained diuresis occurred, which was associated with increased glomerular filtration rate (GFR). However, in one patient, diuresis occurred several hours after the patient was given furosemide; in the other patient, diuresis occurred without diuretics. How can one prove that the first patient's diuresis was produced by furosemide?

After reviewing all the potential problems raised in studies dealing with such a varied syndrome as oliguric ATN, one can understand Muth's conclusion: "The task of discussing the prevention or treatment of this unpredictable, usually self-limited, sometimes unrecognized syndrome of various and often unknown etiologies may be as perplexing as the problem itself."<sup>47</sup>

### In Diagnosing ATN

In patients in whom other causes of ARF have been ruled out, it is necessary to distinguish prerenal azotemia from acute tubular necrosis. Merrill<sup>3</sup> proposed that a positive response to the loop diuretics distinguished the two syndromes. However, there are no data available which show the sensitivity of this "diuretic challenge test" (the percentage of patients with prerenal azotemia in whom diuresis occurs), or its specificity (the percentage of patients with ATN in whom diuresis does not occur).

Others have emphasized the importance of laboratory tests in this regard. The first urinary sediment study is diagnostic of ATN in 80 percent of patients, showing many darkly pigmented,

TABLE 1.—Use of Furosemide in Patients With Acute Renal Failure in Four Controlled Studies

Reference and No. of Patients*	Assignment (comparison)†	Proof of Oliguric ATN (duration)	Furosemide Dose	Rate	Adverse Reactions	Duration of Oliguria (days)	Duration of Azotemia	Dialysis Requirement	Time to a Diuresis of >1,500 ml/day	Mortality
Berionadi <sup>13</sup> C = 12 T = 12	Not random (similar cause)	Inadequate (3-6 days)	60-480 mg every day	?	Numbness (1)	10.6 vs 14.5 (NTFS)†	?	8 vs 12 patients (NTFS) [P>0.2]§	?	3 vs 6 patients (NTFS) [P>0.2]§
Cantarovich <sup>14,15</sup> C = 13 T <sub>1</sub> = 19 T <sub>2</sub> = 15	Not random (similar cause, duration)	Inadequate (average 2 days)	600 mg every day (fixed dose) 100-3,200 mg every day (progressive dose)	5 mg/min 5 mg/min	Tinnitus if rate >14 mg/min	NSD <sup>1</sup> 5.7 vs 15.0 (P<0.02)	NSD NSD	NSD 2.8 vs 8.8 sessions (P<0.02)	NSD 9.7 vs 21.8 days (P<0.005)	NSD NSD
Cantarovich <sup>15</sup> C = 19 T = 39	Not random (similar duration)	Adequate (average 2 days)	2,000 mg every day	4 mg/min	0	7.0 vs 14.0 (P<0.005)	NSD	4.9 vs 9.6 sessions (P<0.05)	10.0 vs 19.6 days (P<0.02)	NSD
Kleinknecht <sup>50</sup> C = 33 T = 33	Random (similar cause, duration, severity)	Adequate (variable)	1.5-6 mg/kg of body weight every 4 hours	Over a few minutes	Transient tinnitus, deafness (several patients)	NSD	NSD	NSD	4.0 vs 8.3 days (P<0.01)	NSD

ATN = acute tubular necrosis; NSD = no significant difference; NTFS = not tested for significance

\*Number of patients in treatment (T) and control (C) groups

†Method of patient assignment to treatment and control groups, and comparison between groups.

‡Not tested for significance by author.

§P value by one-tailed Fisher exact test.

¶No significant difference at  $\alpha = 0.05$  level.

granular casts.<sup>1</sup> Miller and co-workers<sup>48</sup> have recently shown the sensitivity (90 percent) and specificity (96 percent) of two urinary indices, the renal failure index (RFI) and the excreted fraction of filtered sodium ( $FE_{Na}$ ) study, in diagnosing acute tubular necrosis. The equations for the two indices are as follows:

$$RFI = \frac{U_{Na}}{U/P_{Cr}} \text{ and } FE_{Na} = \frac{U/P_{Na}}{U/P_{Cr}} \times 100$$

$U_{Na}$  = urine sodium

$U/P_{Cr}$  = urine/plasma creatinine

$U/P_{Na}$  = urine/plasma sodium

Because these noninvasive tests have proven sensitivities and specificities, and no associated morbidity, the diuretic challenge test is not indicated when attempting to differentiate prerenal azotemia from acute tubular necrosis.<sup>1,49</sup>

### In Treating ATN

The recent literature includes numerous reports concerning the therapeutic use of loop diuretics in patients with acute renal failure. Among these are 4 controlled studies (Table 1)<sup>13-15,50</sup> and 13 uncontrolled series of patients (Table 2).<sup>4-12,16,47,51</sup> The number of patients in each of the 17 studies ranged from 2 to 49. Causes of ARF other than ATN were excluded in only ten of the studies. Duration of renal failure before beginning treatment varied from several hours<sup>8,47</sup> to many days,<sup>6,51</sup> and size of dose, frequency and rate of administration also varied widely. All doses were given intravenously except in Epstein's study, where furosemide was infused directly into the renal artery.<sup>51</sup>

No author ascertained ototoxicity using audiometry; all relied on patient complaints or routine physical examinations. Even so, five authors reported transient or permanent deafness in some of their patients. And in one patient, spontaneous atrial fibrillation developed while the patient was receiving a bolus of furosemide through a central venous line.<sup>17</sup>

The 13 uncontrolled series attempted to answer one important question: Does the use of a loop diuretic produce a sustained diuresis in patients with ATN? Of the 275 patients, a sustained diuresis of greater than 1,000 ml per 24 hours was reported in 120 (44 percent).

However, there are serious difficulties in interpreting these data. First, seven of the studies either failed to show that all patients had ATN, or admittedly included patients with ARF resulting

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from other causes (see Table 2): And in two of the studies, it is not stated whether the diuresis was sustained. The time between administration of the diuretic and subsequent diuresis was not described in three studies, and in a fourth it was as long as 96 hours. More important, in no study could it be proved that an observed diuresis occurred as a direct result of administration of the drug.

It is also important to know whether diuresis is accompanied by a fall in the serum creatinine level, indicating an increase in glomerular filtration rate (GFR). Six series did not include data on this point. In the seven which did, sustained diuresis was associated with a fall in creatinine levels in fewer than half the cases. In the one controlled study that considered this question, sustained diuresis "early" in the course of ATN

was noted in 3 of 33 treatment patients in 2 of 33 control patients.<sup>50</sup> Finally, an associated increase in GFR was noted in only two of these five patients.

The four controlled studies examined differences between control and treatment groups with respect to five major factors: duration of oliguria, duration of azotemia, dialysis requirements, time to onset of a diuresis greater than 1,500 ml per day and mortality. However, several problems in these studies should be mentioned. Patient assignment was random in only one study.<sup>50</sup> Beroniade<sup>13</sup> matched control patients to treatment patients with ARF of similar cause and duration. Patient assignment in Cantarovich's two studies<sup>14,15</sup> is unclear, although random assignment was not used. Also, ATN as the cause of acute renal failure was not sufficiently shown in two of the studies.<sup>13,14</sup>

TABLE 2.—Use of Diuretics in Patients With Acute Renal Failure in 13 Uncontrolled Series

Reference	No. of Patients	Proof of Oliguric ATN (duration)*	Drug			Adverse Effects	Induction of Sustained Diuresis (onset)†	Associated Decrease in Creatinine
			Name	Dose‡	Rate			
Auger <sup>4</sup> . . . . .	2	Adequate (1-5 days)	EA M	50 mg×1 or 2 25 mg×1 or 2	over 15 min	0	2/2 (<4 hours)	?
Castro <sup>5</sup> . . . . .	14	Adequate (>24 hours)	FR	500 mg×1	4 mg/ min	?	5/14 (<24 hours)	?
Desmonts <sup>6</sup> . . . .	8	Adequate (1-14 days)	FR	20 mg every hour	?	0	8/8 (12-96 hours)	?
Fries <sup>7</sup> . . . . .	22	Inadequate (?)	FR	500-1,000 mg every day	3 mg/ min	0	13/22 (<24 hours) [?sustained]	?
Sullivan <sup>8</sup> . . . . .	3	Inadequate (12-24 hours)	FR	80-2,000 mg every 4 hours	?	0	2/3 (<24 hours)	?
Olmer <sup>9</sup> . . . . .	24	Inadequate (?)	FR	100 mg every 4 hours	?	0	11/24 (<24 hours) [?sustained]	?
Humbert <sup>10</sup> . . . .	22	Inadequate (?)	FR	125 mg every 3 hours	?	0	14/22 (<6 hours)	no
Kjellstrand <sup>11</sup> . .	13	Inadequate (3-216 hours)	EA M	1 mg/kg of body weight×1 variable	over several min	t. deafness (1) p. deafness (1)	4/13 (<4 hours)	no
Beaufils <sup>12</sup> . . . .	41	Adequate (?)	FR	160 mg every 6 hours	?	t. deafness (1)	27/41 (<3 hours)	yes in 11/27
Brown <sup>16</sup> . . . . .	49	Adequate (?)	FR	250-1,000 mg×1	<33 mg/ min	?	11/49 (?)	yes in 4/11
Stott <sup>17</sup> . . . . .	29	Adequate (?)	FR	250-500 mg×1	<50 mg/ min	A. fib. (1) tinnitus (most)	5/29 (?)	yes in 3/5
Muth <sup>47</sup> . . . . .	42	Inadequate (<24 hours)	FR	100-1,000 mg every 3 hours	<16 mg/ min	0	17/42 (?)	yes in 7/17
Epstein <sup>51</sup> . . . . .	6	Adequate (2-9 days)	FR	280 mg×1 [intra-arterial]	10 mg/ min	?	1/6 (3 days)	yes in 1/1

A. fib. = atrial fibrillation; ATN = acute tubular necrosis; EA = ethacrynic acid; FR = furosemide; M = mannitol; p. = permanent; t. = temporary

\*Duration of oliguria at time diuretics were begun.

†Dose size and frequency.

‡Time of onset of sustained diuresis after first dose of diuretic.

Despite these problems, these studies provide the best data available at present.

**Duration of oliguria.** Beroniade<sup>13</sup> found that patients in the treatment group had a shorter average duration of oliguria than those in the control group (10.6 versus 14.5 days). He did not test these results for statistical significance, and there are not sufficient data to allow the reader to do so. Cantarovitch employed three treatment protocols in his two studies. In the two protocols with the highest doses of furosemide, he found that there was significant shortening of the average duration of oliguria in the treatment group.<sup>14,15</sup> The structural flaws in these two studies were reviewed above. In the only randomized controlled study, Kleinknecht<sup>50</sup> found a nonsignificant trend favoring treatment (11.9 versus 15.6 days average duration).

**Duration of azotemia.** None of the controlled studies showed a significant difference in average duration of azotemia between the treatment and control groups, although in three of the studies there were slight trends favoring the treatment groups.<sup>14,15,50</sup>

**Dialysis requirements.** Beroniade<sup>13</sup> found that 8 of 12 treatment patients required dialysis, compared with 11 of 12 control patients. However, he did not define his criteria for dialysis, nor did he test his results for significance. However, using Beroniade's data, one may carry out a one-tailed Fisher exact test,<sup>52</sup> which shows that this result is not significant ( $0.2 < P < 0.5$ ). Cantarovitch<sup>14,15</sup> defined conditions for dialysis, and found that treatment patients required significantly less dialysis than control patients. Kleinknecht<sup>50</sup> also defined dialysis requirements, and found a nonsignificant trend favoring treatment.

**Time to onset of a diuresis greater than 1,500 ml per day.** In the three studies which discussed this criterion of success, it appears that high doses of furosemide significantly shorten (by about 50 percent) the average time required to achieve a diuresis greater than 1,500 ml per day.<sup>14,15,50</sup>

**Mortality.** Fewer patients died in the treatment group in Beroniade's study (3 of 12, versus 6 of 12), but he did not test these results for significance.<sup>13</sup> Again, the application of a one-tailed Fisher exact test shows lack of significance at the  $\alpha = 0.05$  level. In the other three studies, no significant differences in mortality were found between treatment and control groups, nor were trends favoring either group seen.

## Discussion

More information is needed regarding the risks of using high-dose diuretic therapy in patients with ARF. It has been suggested that renal failure may be a precondition for the occurrence of diuretic-induced deafness because this underlying condition was present in all the patients studied in whom deafness occurred. However, because acute renal failure is the indication for high-dose diuretic treatment in almost all cases, renal failure may be associated with deafness only as a confounding variable. Also, synergistic ototoxicity between these diuretics and aminoglycosides has been postulated but not proved. Finally, the incidence of transient and permanent deafness occurring in patients with ARF when these diuretics are given in large doses is not known. One can only extrapolate that the incidence is probably higher than that seen in healthier patients with congestive heart failure or edema who receive conventional orally given doses of the diuretics.

Similarly, our knowledge of the possible benefits of using these two drugs in patients with oliguric ATN is incomplete. It is fairly certain that treatment with furosemide shortens the average duration of oliguria, and treated patients achieve a urine output greater than 1,500 ml per day earlier than control patients. While this earlier diuresis would facilitate volume management, it is not associated with a shorter average duration of azotemia. Thus, it appears that some treated patients convert from a state of oliguric ATN to a state of nonoliguric ATN.

Recently, Anderson and co-workers<sup>53</sup> showed that patients with nonoliguric ATN had a significantly lower incidence of morbidity (gastrointestinal bleeding, septicemia, acidemia, and neurological abnormalities) and mortality than patients with oliguric ATN. This difference held true for patients with spontaneous nonoliguric ATN as well as for patients in whom oliguric ATN changed to nonoliguric ATN after one or more intravenously given doses of furosemide (2 to 10 mg per kg of body weight). Of 56 patients who had oliguria, 40 received furosemide in doses of varying sizes; in 18 of these 40 there was a change to nonoliguric ATN. The patients in whom there was response to furosemide had significantly less renal impairment than those in whom there was no response to furosemide. Despite these promising findings, the authors concluded that "the value of the common clinical use of furosemide in treating the oliguric

patient remains to be determined by prospective controlled trials."<sup>53</sup>

It appears likely that in patients treated with furosemide, considerably fewer dialysis sessions are needed, on an average, than in control patients. In the four controlled studies, trends favoring the treatment group were present in two, and in the other two studies, differences in average dialysis requirements were significant. Because hemodialysis is expensive and associated with some morbidity, a decrease in dialysis requirements would be advantageous.

Finally, none of the four controlled studies found a significant difference in mortality between treatment and control groups. On the other hand, power analysis shows that none of these studies included enough patients to achieve statistical significance at the  $\alpha=0.05$  level, even if a large difference in mortality existed. For example, in Kleinknecht's study,<sup>50</sup> mortality in the control group was 12 of 33 patients, or about 35 percent. If the mortality in the treatment group were really 25 percent (a clinically important reduction), each group would require 367 patients to have an 80 percent chance ( $\beta=0.20$ ) of detecting such a difference at the  $\alpha=0.05$  level.<sup>54</sup> Stated another way, with only 33 patients in each group, mortality could drop from 35 percent in the control group to 5 percent in the treatment group, and the study would still have only a 70 percent chance ( $\beta=0.30$ ) of detecting this difference at the  $\alpha=0.05$  level.<sup>54</sup>

### Summary

There is no reason to administer either ethacrynic acid or furosemide to persons as an aid to diagnosing oliguric ATN. In patients shown to have this syndrome, treatment with large doses of furosemide given intravenously, will shorten the average duration of oliguria, and shorten the time until a daily urine output of 1,500 ml occurs. Requirement for dialysis probably will be modestly decreased. However, there is no evidence from controlled studies that the average duration of azotemia is reduced by this treatment or that mortality is decreased, although these studies have large  $\beta$ -errors. It is possible that furosemide may convert early oliguric ATN to nonoliguric ATN, with improved prognosis for patients, although this remains to be proved in prospective controlled studies.

The known and potential benefits must be weighed against the known risks of these drugs, most importantly, the induction of permanent deafness. In doses of less than 100 mg, furosemide is probably safer than ethacrynic acid.<sup>35</sup> There is no reason to believe this does not hold true for larger doses as well. Using rates of administration less than 15 mg per minute probably will reduce the incidence of deafness. Thus far, this rate has not been shown to reduce the possible efficacy of furosemide in patients with ATN. While more data are needed concerning this therapeutic dilemma, physicians who decide to administer furosemide as a treatment for patients with oliguric ATN should be aware of the risks of this therapy, and strive to minimize them.

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